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Comparative assessment of allergic reactions to COVID-19 vaccines in Europe and the United States

To the Editor,

Among the rare complications that may compromise vaccine acceptance are allergic reactions.[1–3] Recently, we demonstrated that anaphylaxis rates associated with COVID-19 vaccines are within the range of those observed earlier with other vaccines, as indicated by passive reporting systems.[4] Herein, we aimed to comparatively assess the incidence and potential underlying causes of the most common allergic reactions post-COVID-19 vaccination in Europe and the United States (US). To our knowledge, such a comparison has not been performed before.

Allergic reaction data following COVID-19 vaccination reported from Week 52/2020 to Week 39/2021 were collected from EudraVigilance for the European Economic Area (EEA) and from Vaccine Adverse Event Reporting System (VAERS) for the United States and analyzed for all licensed vaccines. These included mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), AD26.COV2.S (Janssen/Johnson & Johnson), and the not yet licensed in the US ChAdOx1-S (Oxford/AstraZeneca). Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Vaccine composition was examined to identify potential allergic triggers.

The most common allergic reactions after COVID-19 vaccination were anaphylactic reactions, with an overall incidence of 9.91/million doses (EEA: 13.69/million/US: 4.44/million, Figure 1). Anaphylactic shock followed, with much lower rates (overall incidence: 1.36/million, EEA: 2.01/million/US: 0.41/million). Other allergic symptoms post vaccination, which were infrequently reported in the two databases, included, among others, "anaphylactoid reactions" and "allergic edema." Sampath et al. and Alhumaid et al. also reported a similar spectrum of allergic and possibly non-allergic reactions post vaccination.[2,5]

Higher anaphylactic reaction rates have been reported after the first than the second dose, especially when prior anaphylaxis was present, but that was not always the case.[5,6]

The incidence of anaphylactic reactions reported in EudraVigilance varied considerably by vaccine and was threefold to fourfold higher for BNT162b2 or mRNA-1273 compared with VAERS. AD26.COV2.S-associated anaphylaxis did not differ between databases. The very low incidence of anaphylactic shock also varied by vaccine, particularly as captured in EudraVigilance.

Considering vaccine platforms, the incidence of anaphylactic reactions post adenovirus-vectored vaccination was higher compared with mRNA-based vaccines (EudraVigilance: 15.62/ vs. 13.36/million and VAERS: 6.79/ vs. 4.34/million doses). Anaphylactic shock incidence rates were also higher for vectored compared with mRNA vaccines (EudraVigilance: 3.14/ vs. 1.81/million and VAERS: 1.20/ vs. 0.38).

Detailed demographic data and outcomes of anaphylactic reaction and anaphylactic shock cases post-COVID-19 vaccination are presented in Tables S1 and S2, respectively. The vast majority of cases affected females (82% of anaphylactic reaction/75% of anaphylactic shock reports). The reasons why women have been implicated more frequently in hypersensitivity reactions throughout cohorts remain unknown.

With regard to age, different patterns are evident. In EudraVigilance, both types of anaphylaxis were more common among working age (18–64 years) and older individuals; in VAERS, anaphylactic reactions were more frequent among subjects aged 30–59 years (69%), while the very rare anaphylactic shock cases were distributed across age groups.

Regarding outcome, the vast majority of cases were resolved or resolving (90.0% of anaphylactic reaction/81.7% of anaphylactic

shock cases as captured in EudraVigilance, Table S1). The disease course was complicated (life threatening or leading to permanent disability) in 25.5% of anaphylactic reaction and 31.3% of anaphylactic shock cases as captured in VAERS (Table S2). Fatalities from allergic reactions post-COVID-19 vaccination were extremely rare and twofold to sixfold higher for vectored than mRNA vaccines in both databases (Table 1).

The anaphylactic reactions and anaphylactic shock cases reported to EudraVigilance compared with VAERS indicated significant differences to exist between reporting systems, vaccine platforms, and manufacturers. Conceivably, the reported variability may reflect population differences in the degree of sensitization to ingredients prior to vaccination and differences in the prevalence of atopy, which has been linked to anaphylactic incidents post vaccination.[2,7] Differences in implementation between the two reporting systems could also contribute to the observed differences between databases.

The cause(s) that may trigger allergic reactions after vaccination remain elusive.[2] Potential contributing factors include the following: (i) components of the final pharmaceutical product (i.e., the active ingredient and excipients); (ii) impurities or "related materials" unintentionally present in the final formula;[1] and (iii) the packaging material, especially the rubber stopper.[2] Cross-reactivity has been reported upon exposure between two of the main excipients of mRNA and vectored vaccines (polyethylene glycol 2000 and polysorbate 80, respectively).[8] If true, should we anticipate increased anaphylaxis rates following first time or booster vaccination with vaccines of different platforms according to the so-called heterologous vaccination (mix-and-match) approach?

A potential limitation of the study may be the likely underreporting of allergic reactions, including anaphylaxis that generally holds for passive surveillance systems; nonetheless, this may not hold for COVID-19 vaccines that have been under scrutiny by regulators and under the watchful eyes of healthcare professionals and the public since the beginning of their deployment. Other potential limitations, also related to passive reporting systems, entail possible reporting errors (e.g., duplicate or incomplete records), as well as the fact that recorded events only show temporal and not cause–effect relationships. In addition, the terminology used for the categorization of anaphylaxis post vaccination possibly introduces mechanistical explanations that may not be accurate. Nevertheless, for anaphylaxis and Guillain–Barré syndrome, the sensitivity of VAERS was found to be comparable to previous estimates for detecting important adverse events following vaccination.[9]

Our pragmatic analysis is based on imperfect, but real-world data of two of the world's largest and most reliable vaccine adverse event

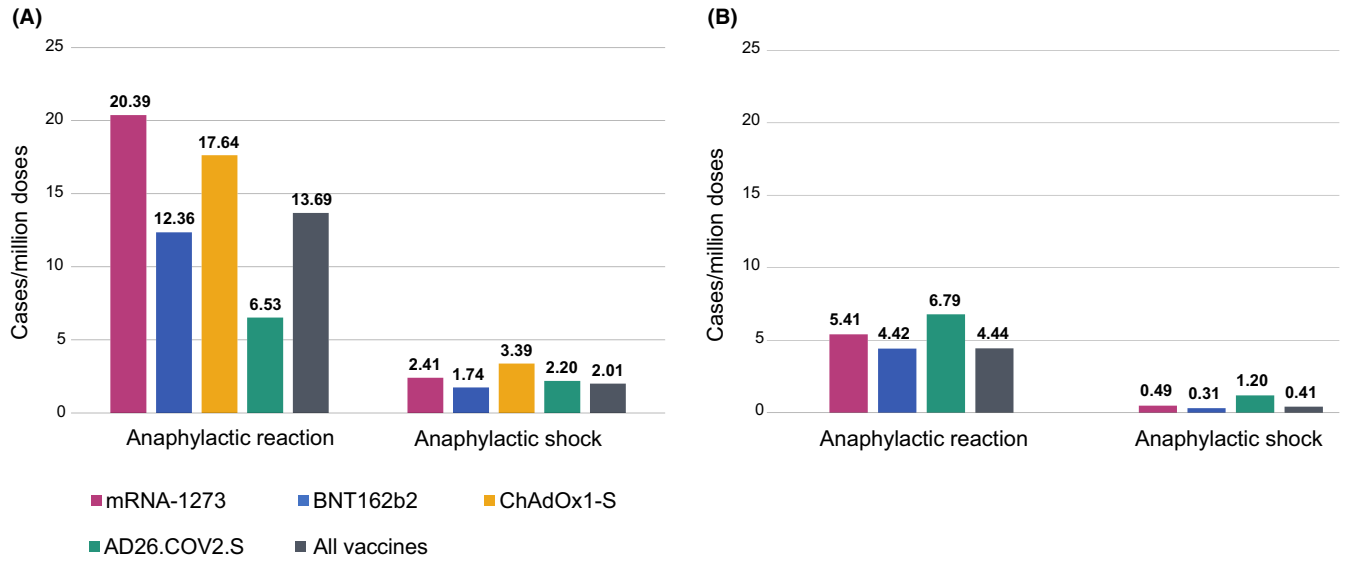

FIGURE 1 Incidence of anaphylactic reaction and anaphylactic shock post-COVID-19 vaccination for licensed vaccines reported in EudraVigilance (A) and VAERS (B) databases from Week 52, 2020 to Week 39, 2021. Rates were estimated by normalizing the number of reported cases to administered vaccine doses (and expressed per million doses)

TABLE 1 Fatality incidence related to anaphylactic reaction, anaphylactic shock, and their sum post-COVID-19 vaccination with licensed vaccines reported in EudraVigilance for the European Economic Area and in VAERS for the United States from Week 52, 2020 to Week 39/2021 by vaccine platform

	Fatalities/100 million administered vaccine doses					
	Anaphylactic reaction		Anaphylactic shock		Sum	
Platform	mRNA	Vector	mRNA	Vector	mRNA	Vector
Database						
EudraVigilance	5.15	10.70	1.85	10.70	7.01	21.41
VAERS	1.85	6.66	0.79	0	2.64	6.66

spontaneous reporting systems (EudraVigilance and VAERS). Our estimated rates from VAERS for anaphylactic reactions [4.34 for mRNA vaccines (5.41 for mRNA-1273 and 4.42 for BNT162b2) cases per million vaccinations] are in agreement with those reported largely in individuals with a history of allergy, by the Centers for Disease Control and Prevention (CDC), which were also based on passive spontaneous reporting methods (2.5–11.1 per million vaccinations).[6] We found higher corresponding rates in EudraVigilance (13.36 per million vaccinations for mRNA vaccines overall) and more elevated for mRNA-1273 rather than BNT162b2 (20.39 vs. 12.36 per million vaccinations, respectively). Blumenthal et al.[7] found larger incidence rates of confirmed anaphylaxis to mRNA vaccines using either the Brighton Criteria [10] or the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria[11] (2.47 per 10000 vaccinations).[7] Interestingly, this study also reported more frequently detecting acute allergic reactions with the Moderna rather than the Pfizer-BioNTech vaccine (2.20% [95% CI, 2.06%-2.35%] *vs.* 1.95% [95% CI, 1.79%- 2.13%]; $p = 0.03$).[7]

Relevant investigations in the literature report contradictory results, concluding on higher anaphylaxis incidence for mRNA-1273[7] or BNT162b2.[5] These results emphasize the influence of the chosen datasets on the final conclusion.

Our study revealed differences in anaphylaxis rates as captured in two of the world's largest pharmacovigilance databases between Europe and the United States, as well as between vaccines and vaccine platforms. Understanding the reasons behind true differences could lead to the further optimization of COVID-19 vaccines.

CONFLICT OF INTEREST

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories; holds patents related to vaccinia, influenza, and measles peptide vaccines; received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine; and provides consultative advice on vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Johnson & Johnson/Janssen Global Services LLC, Emergent Biosolutions, Dynavax, Genentech, Eli Lilly and Company, Kentucky Bioprocessing, Bavarian Nordic, AstraZeneca, Exelixis, Regeneron, Janssen, Vyriad, Moderna, and Genevant Sciences, Inc.

These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

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SH, CA, VL, HM, EA, and AT declare no conflict of interest in relation to this work.

AUTHOR CONTRIBUTIONS

SH and CA designed the study, acquired the data, and wrote the manuscript. SH, CA, VL, and HM contributed to data analysis and interpretation. CA, VL, HM, EA, GP, and AT revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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*HLA-DPB1*05:01* genotype is associated with poor response to sublingual immunotherapy for Japanese cedar pollinosis

To the Editor,

Sublingual immunotherapy (SLIT), including that in patients with Japanese cedar (JC) pollinosis, has been shown to significantly improve severe symptoms while lowering the use of anti-allergic drugs; additionally, SLIT can have a persistent long-term effect after discontinuation.[1] Although most patients with allergic rhinitis (AR) respond favorably to SLIT, these therapies are ineffective in ~30% of such patients. Moreover, it can take two years or more to clarify the effectiveness of SLIT for seasonal AR and one year or more for perennial AR. Thus, an assay permitting the identification of patients as responders or non-responders before the implementation of SLIT would be of great value. However, a predictive biomarker for SLIT efficacy is not available for patients with AR.[2] Furthermore, no definitive genetic biomarkers were noted in a European Academy of Allergy and Clinical Immunology (EAACI) position paper on biomarkers for monitoring the clinical efficacy of allergen immunotherapy.[2]

We previously reported that amino acid changes in the allergen-binding pocket of HLA-DPB1 were associated with the development of JC pollinosis and sensitization to JC pollen, and suggested that the structural differences between the antigen-binding pocket of HLA-DPB1 influence sensitization to the allergenic peptide.[3] Cry j 1 is the major antigen of *Cryptomeria japonica* pollen; HLA-DP5 (*DPA1*02:02* and *DPB1*05:01*) has been reported to possess a higher binding affinity to the allergenic peptide of Cry j 1.[4] Therefore, we speculated that the allergen-binding pocket of HLA-DPB1 might be associated with the responsiveness to SLIT among patients with JC pollinosis. The aim of this study was to investigate whether the *HLA-DPB1* gene is associated with SLIT responsiveness in patients with JC pollinosis. Detailed methods are available in an online supplementary.

In total, 219 patients with JC pollinosis were enrolled over various seasons and received standardized JC pollen extract (CEDARTOLEN®, Torii Pharmaceutical Co. Ltd., Tokyo, Japan), and 203 patients were available at the time of peak symptoms in the second season. The characteristics of the patients are shown in Table 1. Responders were defined as individuals with a visual analog scale (VAS) <5, and non-responders as individuals with a VAS ≥5, at the peak symptoms of the season,[5] resulting in 160 responders and 43 non-responders in the second season. The number of JC pollen counts in the pollen season were 2,508 grains/cm^2 in 2015, 3,505 grains/cm^2 in 2016, 2,570 grains/cm^2 in 2017, 5,041 grains/cm^2 in 2018, and 10,933 grains/cm^2 in 2019 (Figure S1); these values and age were adjusted as covariates in the subsequent analysis.

The allele frequencies of *HLA-DPB1* are shown in Table S1. *HLA-DPB1*05:01* was the most frequent allele observed in our study subjects, followed by *HLA-DPB1*02:01* and *HLA-DPB1*09:01* (39.9%, 21.2%, and 9.9%, respectively). Multivariate logistic regression analyses under three models (additive, dominant, and recessive) were performed to assess the relationship between *HLA-DPB1* alleles and the responses of SLIT, with adjustments for age and the count of JC pollen scattering. *HLA-DPB1*05:01* carriers were more frequent in non-responders than in responders in the additive and dominant models (additive model: $p = .023$, $q = 0.115$, odds ratio = 1.75, 95% confidence interval = 1.08–2.85; dominant model: $p = .023$, $q = 0.117$, odds ratio = 2.58, 95% confidence interval = 1.14–5.83;